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LPA Induces Erythropoiesis through Activating LPA Receptor 3.

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ABSTRACT

Lysophosphatidic acid (LPA), an extracellular lipid mediator, exerts multiple bioactivities through activating G-protein-coupled receptors. LPA receptor 3 (LPA(3)) is a member of the endothelial differentiation gene family, which regulates differentiation and development of the circulation system. However, the relationship among the LPA receptors (LPARs) and erythropoiesis is still not clear. In this study, we found that erythroblasts expressed both LPA receptor 1 (LPA(1)) and LPA(3) , and erythropoietic defects were observed in zLPA(3) antisense morpholino oligonucleotide-injected zebrafish embryos. In human model, our results showed that LPA enhanced the erythropoiesis in the cord blood-derived human hematopoietic stem cells (hHSCs) with erythropoietin (EPO) addition in the plasma-free culture. When hHSCs were treated with Ki16425, an antagonist of LPA(1) and LPA(3) , erythropoietic process of hHSCs was also blocked, as detected by mRNA and protein expressions of CD71 and GlyA. In the knockdown study, we further demonstrated that specific knockdown of LPA(3) , not LPA(1) , blocked the erythropoiesis. The translocation of β-catenin into the nucleus, a downstream response of LPA receptor activation, was blocked by Ki16425 treatment. In addition, up-regulation of erythropoiesis by LPA was also blocked by quercetin, an inhibitor of the

β-catenin/TCF pathway. Furthermore, the enhancement of LPA on erythropoiesis was diminished by blocking JAK/STAT and PI3K/AKT activation, the downstream signaling pathways of EPOR, suggested that LPA might play a synergistic role with EPO to regulate erythropoietic process. In conclusion, we first reported that LPA participates in EPO-dependent erythropoiesis through activating LPA(3) .

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